DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

OCT 2 0 1999

Richard F. Moldin
President and CEO
Purepac Pharmaceutical Co.
200 Elmora Avenue
Elizabeth, NJ 07207

Re: Docket No. 99P-2339/CP1

Dear Mr. Moldin:

This responds to your citizen petition, dated July 9, 1999, requesting that the Food and Drug Administration (FDA) immediately approve Purepac Pharmaceutical Co.'s (Purepac's) abbreviated new drug application (ANDA) 74-984. The ANDA references Cardizem CD,[1] extended-release diltiazem hydrochloride capsules (diltiazem). You base your request on your assertion that ANDA 74-752, filed by Andrx Pharmaceuticals, Inc. (Andrx), was not substantially complete and therefore not eligible for 180-day generic drug exclusivity.

Your petition is denied for the reasons discussed below.

I. Background

On November 24, 1995, the Agency accepted ANDA 74-752, filed by Andrx, for diltiazem capsules referencing Cardizem CD. Andrx's ANDA received final approval on July 9, 1998. On September 11, 1998, Andrx submitted a supplemental ANDA which the Agency approved on June 8, 1999. Both the original and the supplemental ANDAs included a paragraph IV certification[2] of noninfringement and/or invalidity as to the patents that claimed Cardizem CD. Andrx was sued for patent infringement[3] by the new drug application (NDA) holder, HMR, and the patent owner. Andrx began commercially marketing its diltiazem product, Cartia XT, on June 23, 1999. The Agency awarded Andrx 180 days of exclusivity under section 505(j)(B)(5)(iv) of the Act. When that exclusivity expires on December 20, 1999, any otherwise eligible ANDA for diltiazem referencing the same listed drug, Cardizem CD, as ANDA 74-752 may receive final approval.

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[1] Sponsored by Hoechst Marion Roussel, Inc. (HMR).

[2] See section 505(j)(2)(A)(vii) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 USC 355(j)(2)(A)(vii)).

[3] See section 505(j)(5)(B)(iii) of the Act.

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On October 15, 1996, the Agency accepted ANDA 74-984, filed by Purepac, for diltiazem capsules referencing Cardizem CD. Purepac's ANDA also contained a paragraph IV certification of noninfringement and/or invalidity as to the patents claiming Cardizem CD. The NDA holder and patent owner sued Purepac for patent infringement. The Agency tentatively approved Purepac's ANDA on October 23, 1998. The 30-month stay in approval resulting from the patent litigation[4] expired on July 10, 1999.

II. Discussion

The fundamental claim in your petition is that Andrx's ANDA was not substantially complete as originally submitted and therefore is not eligible for 180 days of exclusivity (Petition at 16, 24, 31). You state that formulation changes made by Andrx during the ANDA approval process, as well as in the supplemental ANDA, preclude a determination that Andrx's ANDA was substantially complete and therefore defeat Andrx's claim to first applicant status (Petition at 24-29).

The Agency finds that Andrx was the first applicant to submit an ANDA with a paragraph IV certification referencing Cardizem CD and that Andrx's ANDA was substantially complete as originally submitted. Accordingly, it concludes that the award of 180-day exclusivity to Andrx for Cardia XT was proper.

The text of 21 USC § 505(j)(5)(B)(iv) provides for delays of 180 days in the effective approval of subsequent generic drug applications containing paragraph IV certifications where a "previous application has been submitted" containing a paragraph IV certification for the same drug. However, the statute does not define when a "previous application has been submitted" for 180-day exclusivity purposes. As you suggest, the ambiguous text of the statute can be interpreted to deny "previous application" status for an ANDA applicant who, though first to file an application with a paragraph IV certification, files an additional paragraph IV certification based on formulation changes requiring an amendment or supplement to an ANDA after subsequent paragraph IV certifications have been filed by other applicants.[5]

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[4] See section 505(j)(B)(5)(iii) of the Act.

[5] As you are aware, the Agency suggested this interpretation in its recently proposed rule addressing generic drug exclusivity. Specifically, the Agency has proposed to modify both its regulatory definition of substantially complete and its criteria for exclusivity eligibility when an applicant files an additional certification based on a formulation change. See 64 FR 42873 at 42875, August 6, 1999.

As with other interpretive issues arising from the revocation of the "successful defense" requirement for 180-day exclusivity,[6] during the ongoing notice and comment period for the proposed revision of the 180-day exclusivity regulations, FDA continues to rely on its existing regulations to the extent they are relevant, as well as statutory interpretations of the *Mova* court and other courts deciding 180-day exclusivity issues. The existing regulations focus on whether an applicant was first to submit an application that was substantially complete at the time of submission. They define "the applicant submitting the first application" as "the applicant that submits an application that is both substantially complete and contains a certification that the patent was invalid, unenforceable, or not infringed prior to the submission of any other application for the same listed drug that is both substantially complete and contains the same certification." 21 CFR 314.107(c)(2). The regulation further explains that a "'substantially complete' application must contain the results of any required bioequivalence studies, or, if applicable, a request for waiver of such studies."

This focus under the existing regulations on substantial completeness of the application at the time the application is submitted is highlighted in the 1994 preamble to the final rule governing 180-day exclusivity. In response to a comment, the Agency noted that "[a] decision by the agency after receipt of an application that the bioequivalence information is inadequate for approval does not necessarily mean that the application was not *"substantially complete at the time of submission."* (59 FR 50338 at 50354, October 3, 1994) (emphasis added). The Agency has consistently applied this interpretation of the regulation since 1994, and at least one court has supported the Agency's position. (See *Granutec, Inc. v. Shalala*, 1998 U.S. App. LEXIS 6685, Nos. 97-1873, 97-1874 (4th Cir. Apr. 3, 1998).[7]

Because under the Agency consistent interpretation of existing regulations "substantial completeness" has been determined at the time the application is submitted, rather than retrospectively at the time the application is approved, the Agency will not deny exclusivity to Andrx in the circumstances presented here. Andrx was the "applicant submitting the first application" as defined by regulations and therefore was properly eligible for and properly received 180-day exclusivity.

If you have further comments on any issues pertaining to 180-day generic drug exclusivity, the Agency encourages you to submit them to the Dockets Management Branch as described in the proposed rule. (See 64 FR at 42873).

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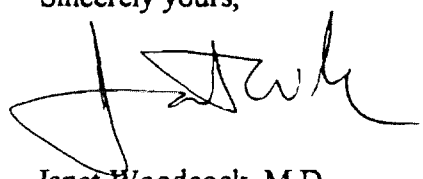
[6] See *Mova Pharmaceutical Corp.* v. *Shalala*, 140 F.3d 1060 (D.C. Cir. 1998) (holding invalid the portion of 21 CFR 314.107(c)(1) that required an ANDA applicant to successfully defend its patent litigation to be eligible for 180-day exclusivity).

[7] The court supported FDA's award of exclusivity to Genpharm, Inc., which filed another paragraph IV certification when it filed an amendment to the original application. The amendment was based on a formulation change to the drug product, Ranitidine.

III. Conclusion

Your petition is denied. However, because the 180-day exclusivity period granted to Andrx for ANDA 74-752 commenced on June 23, 1999, generic versions of diltiazem referencing Cardizem CD, including ANDA 74-984 submitted by Purepac, are eligible for final approval on December 20, 1999.

Sincerely yours,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research